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The effects of cyproterone acetate on statural growth in children with precocious puberty

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Abstract. Forty-four patients (42 f, 2 m) with precocious puberty (31 idiopathic, 1 familial, 7 cerebral, 5 McCune-Albright) were treated with cyproterone acetate for periods of 1–8.75 years in different ($P < 0.05$) daily dosages of 117 ± 6.1 mg/m² per day ($\bar{x}$ ± SEM, group A, N = 20) and 60.8 ± 2.42 mg/m² per day (group B, N = 24). Thirty-three girls had experienced menarche before therapy at a mean age of 4.89 ± 0.42 years. Treatment was started at a chronologic age of 5.45 ± 0.33 years in the girls and 5.74 ± 1.34 years in the boys. At the time of evaluation, 31 of our patients had reached final height. With respect to the effects of treatment on statural growth, the Standard Deviation Scores were retrospectively determined for height, weight, and growth velocity. The initial Bayley-Pinneau height predictions were compared with final height and target height, and the skeletal maturation was studied. There were no significant differences between those parameters in the patients of group A and B or between treated and untreated subjects as far as final height and target height were concerned. It is concluded that cyproterone acetate administered orally at daily doses from 50–150 mg/m² does not improve statural growth of patients with precocious puberty.

Isosexual precocious puberty (IPP) is a rare condition. With respect to its frequency, the idiopathic form predominates the other variants. It is more common in girls than in boys (ratio 3:1, Reiter & Kulin 1972). The incidence of the idiopathic versus the cerebral form is about 7:1 in girls and 1.5:1 in boys. Conditions such as the McCune-Albright syndrome presenting with the triad of sexual precocity, polyostotic dysplasia and cutaneous pigmentation, or other syndromes being also associated with precocious puberty as well as the familial type of the disease are still more infrequent. As for the McCune-Albright syndrome, the underlying mechanism which initiates puberty is controversial (Foster et al. 1984a,b; Lightner et al. 1975).

IPP is induced by a premature activation of the hypothalamo-pituitary-gonadal axis. It is clinically characterized by the onset of pubertal changes at an earlier age than normal, by rapid growth, and an excessive rate of skeletal maturation. These factors are mainly responsible for the impact of this disorder on the patient. Individuals with precocious puberty usually fail to achieve a final height which is adequate to their target height. Although several regimens of hormonal treatment have been introduced in the past (Greenblatt et al. 1971; Helge et al. 1969; Kupperman & Epstein 1962; Menking et al. 1971; Neumann & Hamada 1964), the results have been conflicting with respect to the improvement of ultimate adult stature (Bossi et al. 1973; Greenblatt et al. 1971; Helge et al. 1969; Kauli et al. 1976; Kupperman & Epstein 1962; Lyon et al. 1985; Menking et al. 1971; Rager et al. 1973; Stahnke et al. 1979; Werder et al. 1974). In contrast, it is generally accepted that patients with precocious puberty may benefit from therapy with progestational

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drugs with respect to arrest and reversal of the development of secondary sexual characteristics. One of these agents is cyproterone acetate (CPA) which was first reported by Neumann & Hamada in 1964. CPA had subsequently been introduced for the treatment of precocious puberty in boys and girls, irrespective of aetiology (Helge et al. 1969; Rager et al. 1973; Bossi et al. 1973; Werder et al. 1974; Kauli et al. 1976; Stahnke et al. 1979; Lyon et al. 1985).

In this paper, we present an analysis of CPA treatment in 44 patients with various forms of precocious puberty with special regards to longitudinal growth, skeletal maturation, height prediction, and final height.

Patients and Methods

Definition of IPP

According to clinical criteria, the diagnosis of IPP was established when secondary sexual characteristics appeared before the age of 6 years in girls and 8 years in boys (Bierich 1983). Bone age (BA) had to be accelerated by more than 1 year compared with chronologic age (CA).

Patients, dosage and grouping

The present series comprised 44 patients (42 f, 2 m) with precocious puberty who had been treated with CPA during 1969–1984. The patients, who were followed in three clinics (Depts. of Paediatrics, Universities of Ulm, Tübingen, and Munich), were divided into two groups according to the mean CPA doses applied by mouth twice or three times a day (group A, N = 20, daily CPA dose 117 ± 6.1 mg/m² body surface area (BSA), $\bar{x}$ ± SEM; group B, N = 24, daily dose 60.8 ± 2.42 mg/m², $P < 0.05$).

Variants

With regards to the type of precocious puberty, the diagnosis was idiopathic in 31 patients (29 f, 2 m) and familial in 1 girl. In 7 girls there was a cerebral lesion (5 hydrocephali, 1 suspected hamartoma in the region of the tuber cinerum, 1 tumour around the basal cisterns) associated with precocity. 5 girls presented with the McCune-Albright syndrome.

Protocol

In general, during therapy physical examinations and BA determinations were done every 6 months. The varying numbers of cases at each time of control were caused by two facts: Firstly, BA controls were not always available at every examination. Secondly, the number of patients varied depending on the duration of therapy. After cessation of treatment, all patients underwent follow-up examinations twice a year until they had reached the age of 15–17 years and were discharged from further follow-ups.

Vaginal smears were examined before therapy in most of the girls. In those who were controlled during CPA administration, a reduction of cornified cells was observed.

Methods

All data were evaluated retrospectively. Height was measured using a stadiometer. BA was assessed by the method of Greulich & Pyle (1959). The tables of Bayley & Pinneau (1952) were used for the prediction of adult height. Target height (TH) derived from parental statures was expressed according to Tanner et al. (1970). The absolute values for height, weight and height velocity were transformed into the corresponding SD scores (SDS) using the reference data of the Zurich Longitudinal Growth Study (Prader et al., unpublished). SDS was calculated for CA and BA, respectively. Readers who are not familiar with SDS presentations should be reminded that unchanged SDS values over a period of 2 years signify normal growth and not absence of growth. Since the patients with the various conditions, including those with the McCune-Albright syndrome, did not distinctly differ with respect to the initial age distribution and the therapeutic schedule, the effects on growth were presented graphically by pooling all patients of each group. The graphs and mean values for height, weight, and height velocity were constructed as outlined previously (Sorgo et al. 1982).

Final height (FH) and TH were compared with the corresponding data of two series of untreated patients with precocious puberty reported in the literature (Sigurjonsdottir & Hayles 1968; Thamdrup 1961).

Radiologic studies

None of the patients with precocious puberty associated with intracranial abnormalities underwent craniotomy. The subjects with CNS lesions were investigated either by air-encephalography or by cranial CT scan. The 2 boys with IPP had normal cranial CT scans. Air-encephalograms and CT scans were also performed in 20 other patients with the idiopathic condition and considered to be normal. In the patients with the McCune-Albright syndrome, multiple lesions of fibrous skeletal dysplasia and a markedly thickened base of the skull were evident at radiologic examinations.

Endocrine findings

Before CPA treatment, plasma LH and FSH were determined in 26 patients after GnRH stimulation. In all cases there was a distinct rise of the gonadotropins. In 10 other patients, the sporadically measured LH and

FSH values were in the pubertal range. The levels of the biologically determined gonadotropins from urine were not elevated in 2 subjects. Oestradiol determinations from plasma (RIA) and urine (spectrophotometric, fluorometric, and gaschromatographic methods) revealed elevated values conforming to BA in only 9/15 girls. The remaining patients were found to be normal for age. Plasma testosterone was elevated for age in 1 boy. In general, the range of the hormonal values was wide, displaying no clear differences independent of the type of precocious puberty. During CPA treatment, both in the 'high' and in the 'low' dose treated patients (group A and B), the gonadotropins as well as oestradiol and testosterone returned to the prepubertal range. The secondary signs of pubertal development were reversed, menses and pollutions ceased. On CPA therapy, no clinical symptoms of adrenal hypofunction were observed, although the concentrations of the glucocorticosteroids decreased (Girard et al. 1978).

Statistics

Analyses of significance were performed using non-parametric statistical methods (Wilcoxon test for paired and the Mann-Whitney rank sum test for unpaired samples, Sachs 1978). The hypothesis of independence was tested with the coefficient of correlation according to Spearman. All results were expressed as the mean ± SEM.

Results

Clinical data

Table 1 shows the clinical data of all 44 patients in the two series according to the different daily doses. The mean CA at start of treatment was 5.45 ± 0.33 years for all female patients of group A and B together. CA differed significantly from

Table 1.
Clinical data of patients with various types of precocious puberty grouped according to the mean cyproterone acetate dosage.

N, sex		At start of treatment (years, $\bar{x}$ ± SEM)						Pubertal stage (both groups)	
		Chronological age		Bone age		Menarchal age			
A	B	A	B	A	B	A	B	Breast (range)	Pubic hair
Idiopathic									
11 f	18 f	4.99 ± 0.65	5.83 ± 0.49	8.52 ± 0.92	8.61 ± 0.58	5.27 ± 0.81 (N = 10)	4.52 ± 0.72 (N = 12)	II–IV	II–IV
1 m	1 m	7.08	4.4	11.0	7.0	– *	–	–	II–III
Familial									
–	1 f	–	6.88	–	11.0	–	5.0	II	–
Cerebral									
4 f	3 f	6.22 ± 1.04	3.42 ± 1.34	9.29 ± 0.51	6.66 ± 1.74	6.08 ± 1.19	2.04 ± 0.54 (N = 2)	III–IV	I–II
McCune-Albright									
4 f	1 f	4.77 ± 0.86	6.37	7.93 ± 1.14	8.5	4.19 ± 0.81 (N = 3)	5.33	II–IV	I–II
19 f	23 f	5.21 ± 0.47	5.64 ± 0.46	8.56 ± 0.59	8.58 ± 0.55	5.27 ± 0.56	4.48 ± 0.64	II–IV	I–IV
1 m	1 m	7.08	4.4	11.0	7.0	(N = 17)	(N = 16)		
				< 0.001		n. s.			
Total 42 f		5.45 ± 0.33		8.57 ± 0.4		4.89 ± 0.42		II–IV	I–IV
2 m		5.74 ± 1.34		9.0 ± 2.0		(N = 33)			

Group A = 'high' dose. Group B = 'low' dose, see text. * Emissions at the age of 7 years.

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Results

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		Pubertal stage (both groups)	
Menarchal age			
	B	Breast (range)	Pubic hair
± 0.81 (n = 10)	4.52 ± 0.72 (N = 12)	II–IV	II–IV
*	–	–	II–III
–	5.0	II	–
± 1.19	2.04 ± 0.54 (N = 2)	III–IV	I–II
± 0.81 (= 3)	5.33	II–IV	I–II
n. s.			
± 0.56 (= 17)	4.48 ± 0.64 (N = 16)	II–IV	I–IV
4.89 ± 0.42 (N = 33)		II–IV	I–IV

of 7 years.

initial BA which was 8.57 ± 0.4 years ($P < 0.001$). Among the girls, 33/42 had already experienced menarche at the age of 4.89 ± 0.42 years. There were only slight differences in CA, BA, and menarchal age (MA) with respect to the various types of precocity within each group and between the groups. Concerning the secondary pubertal signs at start of treatment, the breast development was the leading sexual characteristic in girls. One boy had emissions at the age of 7 years, the other presented with pubic hair stage II (Marshall & Tanner 1970).

Patients of group A received 'high' dose CPA therapy (range 97–158 mg/m² BSA per day), those of group B were treated with a 'low' dose regimen (range 48–72 mg CPA/m² per day). The mean duration of therapy did not differ, being 4.86 ± 0.49 years in group A and 4.6 ± 0.39 years in group B.

Anthropometric measurements

The height SD score for CA for all patients decreased from 2.54 ± 0.29 before to 1.28 ± 0.52 SD (n.s.) after 7 years of CPA treatment in group A (Fig. 1A), whereas the corresponding data in group B (Fig. 1B) slightly increased during the same period of time. Considering the BA adjusted data, the height score did not significantly change during CPA therapy either in group A or in group B.

The weight scores for CA and BA displayed a dose-dependent, increasing obesity which was already initially more expressed in patients in group A (Fig. 2A) than in group B (Fig. 2B), though the differences within and between the groups were not significant.

The height velocity scores for CA and BA distinctly decreased under CPA treatment in both groups (Figs. 3A and 3B). Before therapy, height velocity was more accelerated in patients in group A than in group B. During the first therapeutic year, the reduction of growth rate was significant for BA and CA (each P value < 0.05) in group A, whereas a significant decrement for B was not evident until after 4 years of CPA treatment (CA adjusted velocity score, $P < 0.05$). Regarding

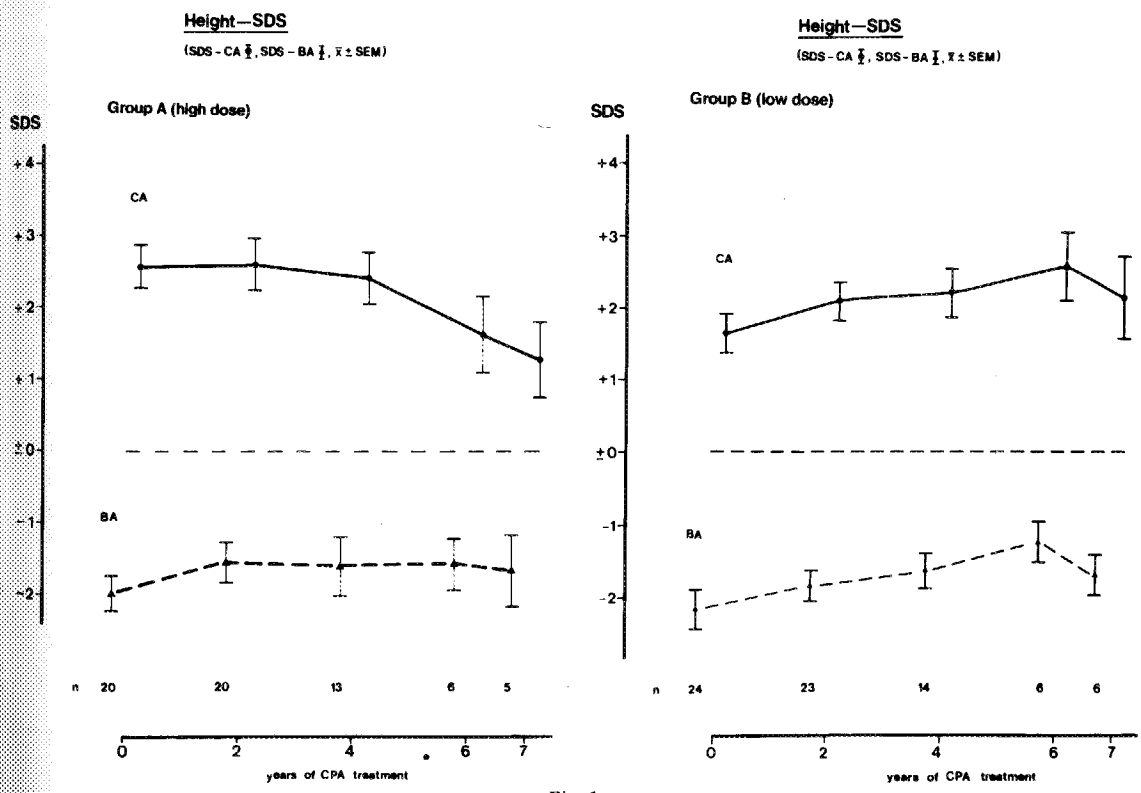

Fig. 1.
Height scores in two groups of patients with precocious puberty during treatment with cyproterone acetate. A) group A = 'high' dose. B) group B = 'low' dose.

Code)

identical periods of therapy, there were no significant differences between the two groups.

Bone maturation

The skeletal maturation (ΔBA/CA) was pronounced in patients in group A (Figs. 4A and 4B), being 2.96 ± 0.51 before therapy and diminishing to 1.31 ± 0.21 years ($P < 0.05$) during the second year of treatment. In group B, the decrement of BA acceleration did not differ statistically between the pretherapeutic and the therapeutic phase. There were no significant differences between the two groups throughout CPA therapy. The ratio expressed by the whole duration of therapy and the total increment of BA within this time was identical for both groups (Table 2).

Final height, target height, and height prediction

There were only slight, insignificant differences in the initial height predictions when comparing the groups with one another (Table 3). As for the patients with the idiopathic variant of precocious puberty, the initial prognoses in group B agreed excellently with FH, whereas in group A, height prediction exceeded FH by about 4 cm. In spite of the low number of cases, it has to be mentioned that the initial predictions in the patients with the McCune-Albright syndrome (group A) differed from FH by about 15 cm. FH was achieved in 31 patients (29 f, 2 m). Height predictions and FH varied significantly from TH in each group and in the whole series ($P < 0.001$).

Achieved FH of all patients was in the lower range of TH and the initial Bayley-Pinneau growth prediction (GP_i-BP).

Correlations

Significant correlations were found between FH and other parameters such as initial CA and BA, initial BP predictions, TH, actual height at the end of CPA therapy, as well as duration of treatment (Table 4).

Outcome of all patients

Regarding the height SD score for BA in all 31 patients of our series up to FH, the SD score was a

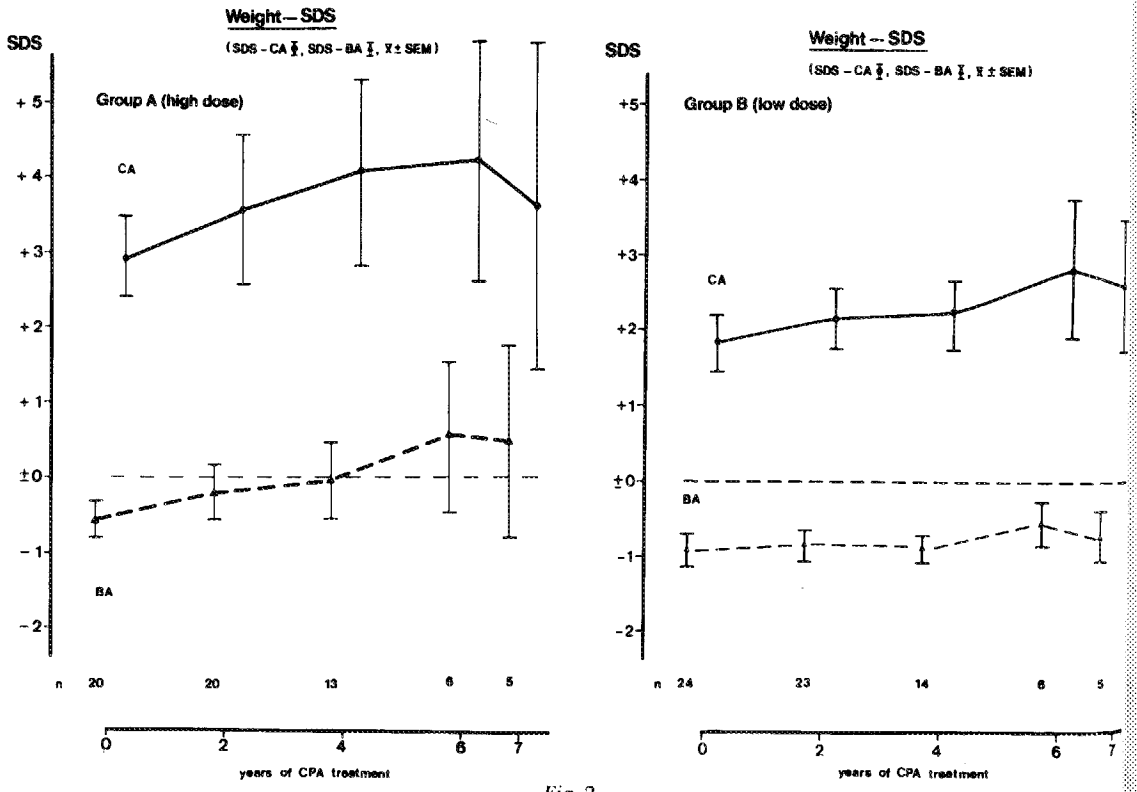

Fig. 2.
Weight scores in two groups of patients with precocious puberty during treatment with cyproterone acetate. A) group A = 'high' dose. B) group B = 'low' dose.

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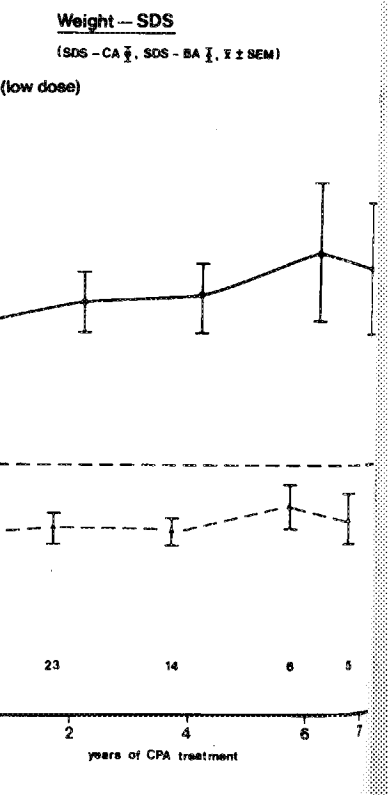

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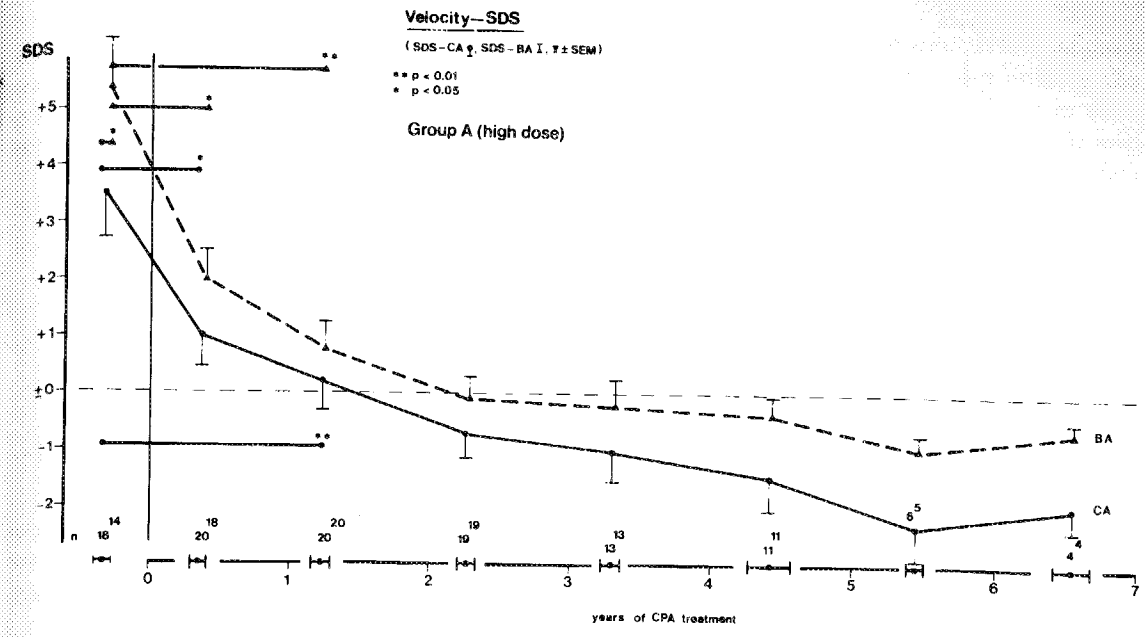

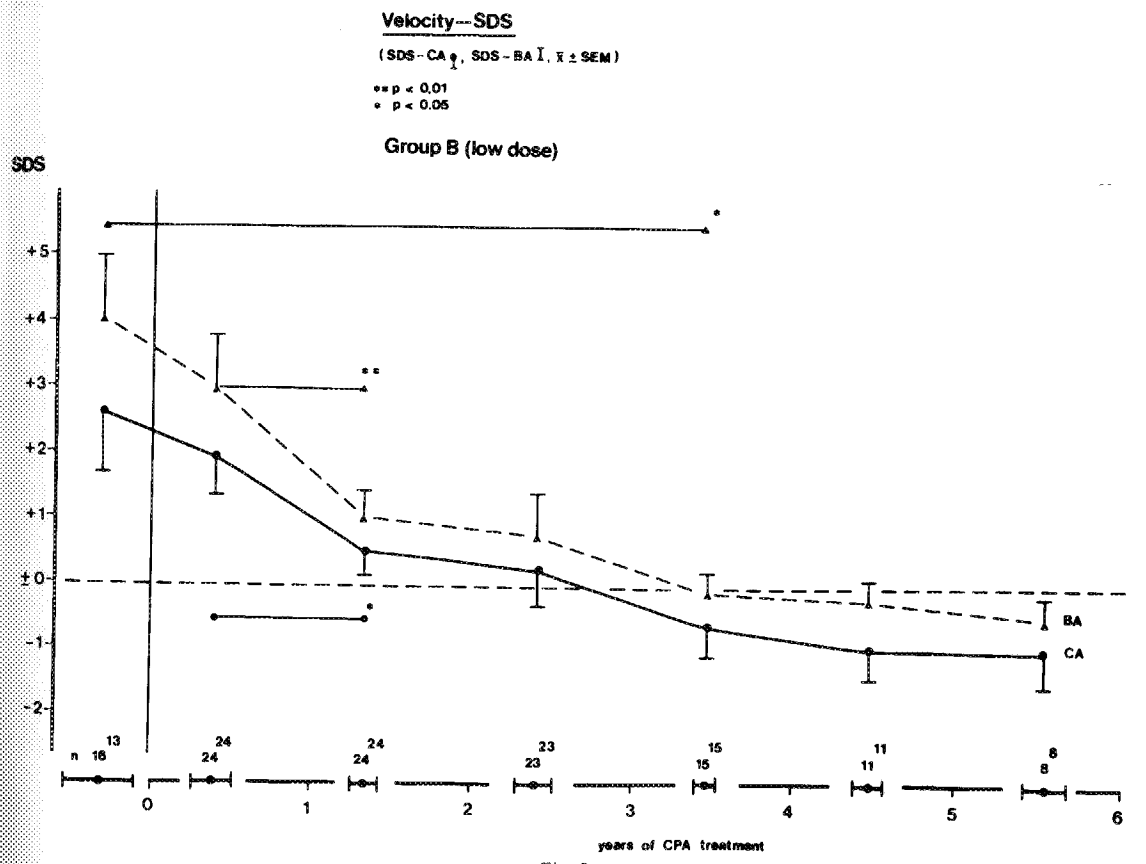

Fig. 3.
Height velocity scores in two groups of patients with precocious puberty during treatment with cyproterone acetate. A) group A = 'high' dose. B) group B = 'low' dose.

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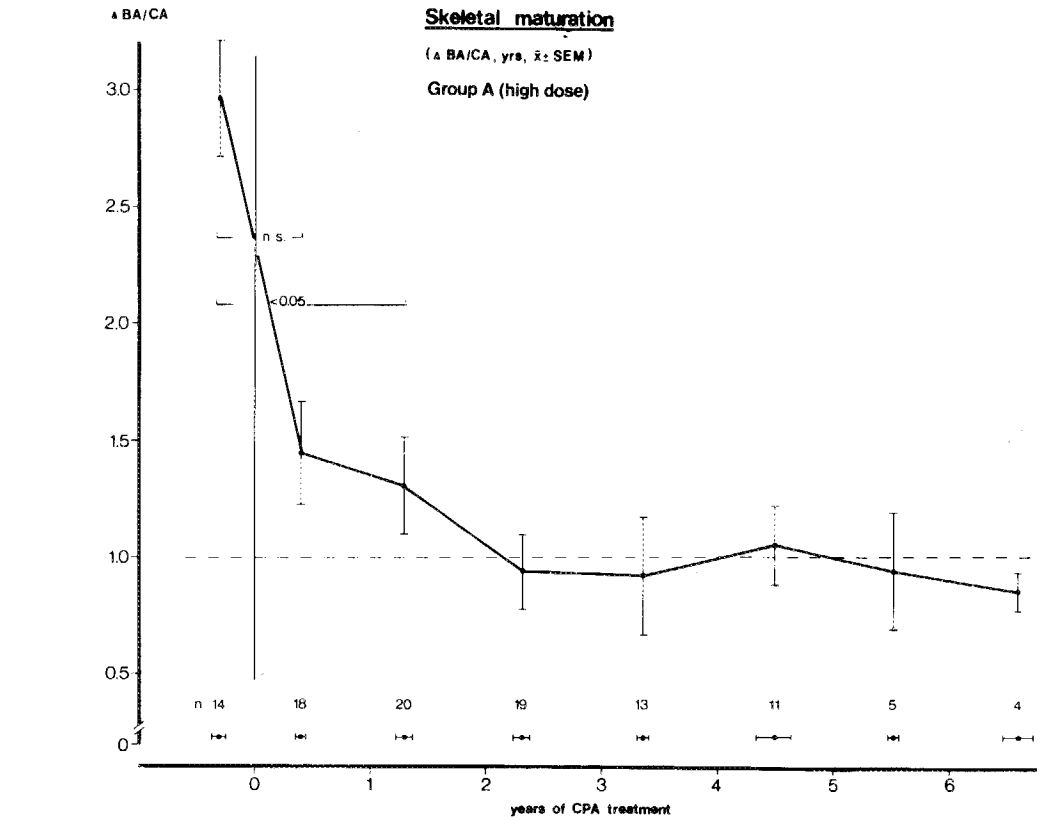


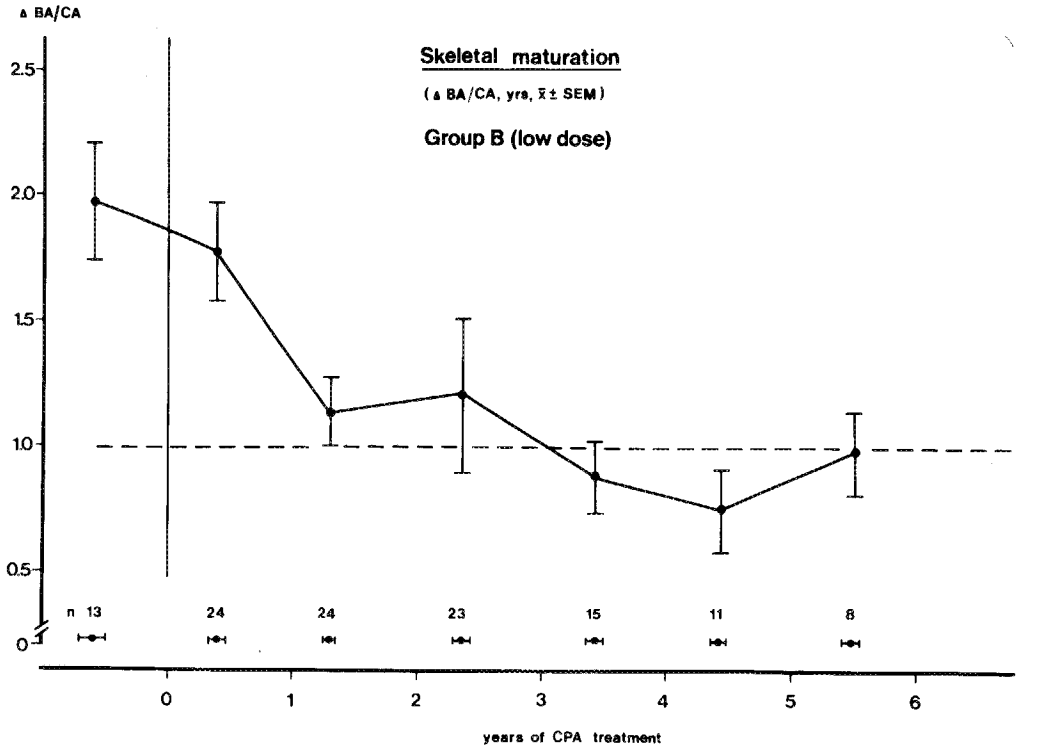
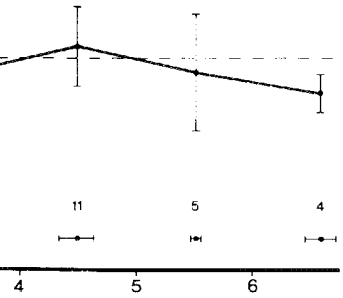
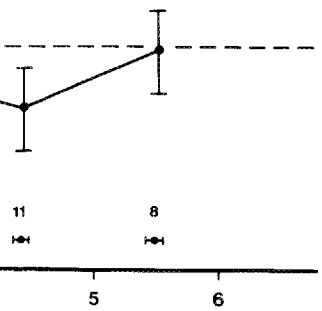


Fig. 4.

Skeletal maturation (Δ BA/CA, years) in two groups of patients with precocious puberty during treatment with cyproterone acetate. A) group A = 'high' dose. B) group B = 'low' dose.





cocious puberty during treatment with
up B = 'low' dose.

Table 2.
Skeletal maturation for the whole period of cyproterone acetate treatment in two groups of patients with precocious puberty. Δ BA_i - BA_e = difference between bone ages at start and at the end of CPA treatment (and similarly for CA).

Group A (N = 20); 'high' dose

$$\Delta \frac{BA_i - BA_e}{CA_i - CA_e} = \frac{4.88}{4.86} \approx 1.0$$

Group B (N = 24); 'low' dose

$$\Delta \frac{BA_i - BA_e}{CA_i - CA_e} = \frac{5.09}{4.6} \approx 1.1$$

very precise measure of height prediction (Table 5). It was obvious that height SDS for BA did not change significantly during and after CPA therapy in the patients with idiopathic IPP. Compared with the other forms of precocious puberty, the deviation from normal was only modest in the 3 patients with the McCune-Albright syndrome. The correlations between the transformed data for all patients at start and at the end of CPA treatment as well as between the latter and FH were significant (each P-value < 0.001), whereas the correlations between the height SDS at start of treatment and at FH were not.

The idiopathic form

Grouping all 23 patients with the idiopathic form according to the daily CPA doses, there were no significant differences between the height scores (group A_1, 126 ± 6.86 mg CPA/m² per day vs group B_1, 69.13 ± 3.16 mg/m² per day, $P < 0.05$, Table 6). Cessation of treatment prior to BA 13 years did not improve FH. This is shown in Table

Table 3.
Bayley-Pinneau height predictions at start of CPA treatment (GP_i-BP), final and target height in two groups of patients with precocious puberty.

N, sex		cm, $\bar{x}$ ± SEM					
		GP_i-BP		Final height		Target height	
A	B	A	B	A	B	A	B
Idiopathic							
11 f	18 f	157.1 ± 2.84	153.33 ± 1.85	153.07 ± 2.29 (N = 7)	153.42 ± 1.25 (N = 14)	160.95 ± 1.46	161.76 ± 1.47
1 m	1 m	171	170	160	166.5	177.5	176
Familial							
–	1 f	–	147	–	154	–	156
Cerebral							
4 f	3 f	150.5 ± 4.18	153.31 ± 7.89	150.67 ± 0.66 (N = 3)	159 (N = 1)	161.38 ± 1.47	164.8 ± 3.16
McCune-Albright							
4 f	1 f	171.04 ± 2.12	164.7	156.25 ± 3.75 (N = 2)	157	170.63 ± 2.31	169.5
19 f	23 f	158.47 ± 2.47	153.55 ± 1.77	153.0 ± 1.48 (N = 12)	153.99 ± 1.09 (N = 17)	163.08 ± 1.34	162.25 ± 1.28
1 m	1 m	171	170	160	166.5	177.5	176
Total 42 f		155.78 ± 1.51	< 0.001 n. s.	153.58 ± 0.87 (N = 29)	< 0.001	162.61 ± 0.92	
2 m		170.5 ± 0.5		163.25 ± 3.25		176.75 ± 0.75	

Group A = 'high' dose. Group B = 'low' dose.

Table 4.
Coefficients of correlation (r_s) according to Spearman between final height and other parameters in 31 patients with various types of precocious puberty.

Final height vs	r_s	P
CA (initial)	−0.35	< 0.05
BA (initial)	−0.32	< 0.05
$\Delta BA_i - CA_i$	−0.17	n. s.
CA (end of treatment)	0.07	n. s.
BA (end of treatment)	0.07	n. s.
BP (initial)	0.55	< 0.001
Target height	0.72	< 0.001
Height (end of treatment)	0.82	< 0.001
Duration of therapy	0.37	< 0.05
Daily dose	0.16	n.s.
Cumulative dose	0.22	n. s.

7, in which all 23 patients with idiopathic precocity were divided into 2 groups by bone age (BA_e) at the end of CPA treatment (group I, BA_e 12.51 ± 0.31 years vs group II, BA_e 14.46 ± 0.38 years, $P < 0.01$).

Treated and untreated patients

The correlation between FH and TH in our series of CPA-treated girls with the idiopathic form of precocious puberty was similar to that in a sample of untreated girls reported by Thamdrup (1961, Table 8). The differences between FH and TH in the untreated cases were nearly the same as in our CPA-treated series.

Discussion

It is accepted that CPA is effective in reducing the clinical manifestations of precocious puberty whereas the effects on statural growth remain a matter of permanent debate.

Our data clearly suggest that the drug administered in daily doses varying from 48–158 mg/m² does not improve the pretherapeutically calculated height predictions: it could be shown that definitely achieved FH did not differ from the FH in untreated patients with precocious puberty reported in the literature (Thamdrup 1961, Sigurjonsdottir & Hayles 1968). CA and BA in the untreated subjects at time of diagnosis were similar to those in the patients in group A and B at start of treatment.

Since the coefficients of correlation between FH and TH in treated and untreated patients (Tables 4 and 8) were nearly identical, the assumption seems to be justified that linear growth in patients with precocious puberty is mainly determined by target height.

To our knowledge, this is the first study which confirms that CPA does not improve statural growth in patients with IPP irrespective of 'low' or 'high' dose treatment (Table 6). Our results are in accordance with those of Werder et al. (1974) who did not find any significant differences between height SDS for BA in 'low' dose (70 mg CPA/m² per day) treated (N = 13) compared with untreated patients (N = 32). The girls from the Zurich sample had been treated at a mean CA of

Table 5.
Height scores for bone age in patients with various types of precocious puberty having been treated with cyproterone acetate and having reached final height.

Type	Height-SDS (BA, $\bar{x}$ ± SEM)		
	At start of treatment	At the end of treatment	At final height (BA ≧ 18 years)
Idiopathic (N = 23)	−2.04 ± 0.24	−2.02 ± 0.2	−1.91 ± 0.18
Familial (N = 1)	−2.4	−1.47	−1.78
Cerebral (N = 4)	−1.63 ± 0.73	−1.95 ± 0.61	−1.99 ± 0.36
McCune-Albright (N = 3)	−0.81 ± 0.29	−1.0 ± 0.13	−1.35 ± 0.37
Total (N = 31)	−1.88 ± 0.21	−1.89 ± 0.17	−1.86 ± 0.14
		$r_s = 0.58^{**}$	$r_s = 0.75^{**}$
		$r_s = 0.26^{*}$	

* n. s. ** $P < 0.001$.

Discussion

that CPA is effective in reducing
anifestations of precocious puberty,
ffects on statural growth remain a
nanent debate.
early suggest that the drug adminis-
doses varying from 48–158 mg/m²
rove the pretherapeutically calcu-
predictions: it could be shown that
eved FH did not differ from the FH
patients with precocious puberty
the literature (Thamdrup 1961;
r & Hayles 1968). CA and BA in the
jects at time of diagnosis were simi-
the patients in group A and B at
ent.
efficients of correlation between FH
ated and untreated patients (Tables
e nearly identical, the assumption
stified that linear growth in patients
us puberty is mainly determined by

wledge, this is the first study which
CPA does not improve statural
ents with IPP irrespective of 'low' or
atment (Table 6). Our results are in
th those of Werder et al. (1974) who
any significant differences between
r BA in 'low' dose (70 mg CPA/m²
ted (N = 13) compared with un-
its (N = 32). The girls from the
had been treated at a mean CA of

recocious puberty having
ned final height.

$\bar{x} \pm$ SEM)	
d nt	At final height (BA ≧ 18 years)
.2	−1.91 ± 0.18
	−1.78
.61	−1.99 ± 0.36
.13	−1.35 ± 0.37
.17	−1.86 ± 0.14
$-r_s = 0.75^{**}$	
*	

Table 6.
Effects of different CPA dosages on height scores for bone age in two groups of patients with idiopathic precocious puberty (group A_1 = 126 ± 6.86 mg CPA/m² per day, $\bar{x} \pm$ SEM; group B_1 = 69.13 ± 3.16 mg CPA/m² per day, $P < 0.05$).

Group	Height-SDS (BA)		
	At start of treatment ($\bar{x} \pm$ SEM)	At the end of treatment	At final height (BA ≧ 18 years)
A_1 (N = 8)	−2.22 ± 0.43	−2.12 ± 0.42	−2.01 ± 0.35
	n. s.	n. s.	n. s.
B_1 (N = 15)	−1.95 ± 0.29	−1.96 ± 0.22	−1.85 ± 0.2
Total (N = 23)	−2.04 ± 0.24	−2.02 ± 0.2	−1.91 ± 0.18
	$r_s = 0.47^{**}$	$r_s = 0.73^{***}$	
	$r_s = 0.15^{*}$		

* n. s. ** $P < 0.025$. *** $P < 0.001$.

6.65 years and had even slightly deteriorated their height scores for BA from −1.28 ± 0.29 ($\bar{x} \pm$ SEM) at start to −1.52 ± 0.32 SD at the end of therapy. In the untreated patients, the SD score remained almost uninfluenced, being −1.53 ± 0.26 at diagnosis and −1.46 ± 0.28 SD at time of analysis (i.e. 6.7 years later). FH and TH in 6 untreated girls with the idiopathic condition were 153.5 ± 3.77 and 161.8 ± 1.51 cm, respectively. Our data agree well with these values ('high' and 'low' dose treated patients together). In comparison to the height scores of Werder's patients, our subjects displayed a more severe deviation from normal and they were younger at time of diagnosis. The untreated sample in Werder's study was not a strict control group, since some of the patients had temporarily been treated with other progestational drugs.

Table 7.
Effect of cyproterone acetate on height scores for bone age in two groups of patients with idiopathic precocious puberty divided according to bone age (BA_c) at the end of treatment. (Group I = BA_e 12.51 ± 0.31 years, $\bar{x} \pm$ SEM; group II = BA_e 14.46 ± 0.38 years, $P < 0.01$).

Group	BA_i (years, $\bar{x} \pm$ SEM)	DD (mg/m²)	Height-SDS (BA)		
			At start of treatment ($\bar{x} \pm$ SEM)	At the end of treatment	At final height (BA 18 years)
Group I (N = 7)	7.77 ± 0.94	88.7 ± 10.5	−1.4 ± 0.4	−1.23 ± 0.33	−1.73 ± 0.32
(BA_e 11–13.33 years)	n. s.	n. s.	n. s.	n. s.	n. s.
Group II (N = 16)	9.33 ± 0.6	89.0 ± 8.3	−2.32 ± 0.54	−2.36 ± 0.4	−1.99 ± 0.42
(BA_e 13.5–15.5 years)					< 0.01
Total (N = 23)	8.86 ± 0.52	89.9 ± 6.53	−2.04 ± 0.24	−2.02 ± 0.2	−1.91 ± 0.18

DD = daily dose. BA_i = initial bone age.

Table 8.
Final height and target height in girls with idiopathic precocious puberty treated with cyproterone acetate compared with untreated patients from other studies.

Treated		Untreated		
Present study (1986) (cm, $\bar{x} \pm$ SEM)		Sigurjonsdottir & Hayles (1968)	Thamdrup (1961)	
Final height	Target height	Final height	Final height	Target height
N = 21 f		N = 21 f	N = 15 f	
$r_s = 0.67^*$			$r_s = 0.64^*$	
153.3 ± 1.1	161.82 ± 1.25	153.2 ± 1.73	150.5 ± 2.14	160.4 ± 1.11
< 0.001			< 0.001	

$^*P < 0.001$.

Bierich (1983) too, did not observe any significant therapeutic effects of CPA on longitudinal growth. With regard to time of discontinuation of therapy, our data contradict Bierich's postulation to stop CPA treatment in girls at a BA of about 12 years in order to have full benefits from pubertal growth spurt. Our data show that cessation of therapy prior to a BA of 13 years has no advantage with respect to improved final height (Table 7). Although our data may suggest to continue CPA treatment up to a BA of 15 years, we observed no significant improvement of FH when compared with the SD scores at the beginning of treatment.

In our series, the coefficients of correlation between FH and the pretherapeutic ages were about r = −0.3 (Table 4), but they were – although significant – too low to be considered a sufficient argument against the hypothesis of Murram et al. (1984) who stated that FH still deteriorated in those patients whose puberty started before the age of 5 years. On the other hand, the relations between FH and pretherapeutic age were limited by the insignificant correlation between $\Delta BA_i - CA_i$ and FH (r = −0.17, Table 4). Consequently, they could not be interpreted in favour of Bierich (1983) either. He found better final heights in those patients treated at an earlier age.

According to a recent review by Lyon et al. (1985), daily doses of 50–100 mg of CPA had no effect on growth in 26 girls with IPP.

A better outcome with respect to height prediction was advocated by Helge (1973) for those patients who had been treated 'early and long enough' with doses ranging from 60 to 100 mg CPA/m² per day. The mean BP predictions changed from 150.4 before to 153.0 cm in 9 patients with IPP after cessation of therapy. A probable improvement of height predictions was also supposed by Rager et al. (1973) in 9 patients with precocious puberty after administration of CPA at daily doses of 100 mg/m². Bossi et al. (1973) described improved height predictions in 5 patients with precocity treated with mean daily doses of 60 mg CPA/m². The authors suggested that the ratio between the increment of height age to the increment of BA might afford more reliable predictions in IPP than the tables of BP. However, it has been unequivocally demonstrated by Zachmann et al. (1978) that BP predictions were fairly appropriate in subjects with precocious puberty. As for the 'low' dose treated patients with the idiopathic form we could confirm a sufficient agreement between pretherapeutic BP predictions and FH (Table 2). For those receiving 'high' dose therapy, it may be speculated whether FH was overestimated or FH – as a consequence of the disease or of the treatment – remained below initial predictions. It should be kept in mind, however, that in the individual case, the prediction error may by considerable. In our experience, the statements of Kirkland et al. (1981) are unusual in that they found final heights of 161 ± 2.6 cm ($\bar{x} \pm$ SEM) in 11 patients with IPP, with prediction errors amounting up to ± 10 cm when calculated by the BP method 4 to 6 years before FH. Kauli et al. (1976) treated 29 patients with precocious puberty with various CPA regimens and observed a beneficial effect on linear growth

berty treated with cyproterone
her studies.

reated		
Thamdrup (1961)		
height	Target height	
N = 15 f		
$r_s = 0.64^*$		
± 2.14	160.4 ± 1.11	
< 0.001		

doses ranging from 60 to 100 mg
day. The mean BP predictions chan-
9.4 before to 153.0 cm in 9 patients
r cessation of therapy. A probable
of height predictions was also sup-
ger et al. (1973) in 9 patients with
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of 100 mg/m². Bossi et al. (1973)
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ecocity treated with mean daily doses
./m². The authors suggested that the
the increment of height age to the
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etween pretherapeutic BP predic-
(Table 2). For those receiving 'high'
it may be speculated whether FH
ated or FH – as a consequence of
of the treatment – remained below
ions. It should be kept in mind,
in the individual case, the predic-
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ements of Kirkland et al. (1981) are
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ors amounting up to ± 10 cm when
the BP method 4 to 6 years before
al. (1976) treated 29 patients with
berty with various CPA regimens
a beneficial effect on linear growth

only in patients with a BA of less than 11 years. Stahnke et al. (1979) claimed that the CPA treatment was effective on growth and bone maturation at mean doses of 65 mg/m² per day. In 16 girls with IPP, the BP predictions improved from 150 ± 9.1 ($\bar{x}$ ± SD) before to 153.9 ± 9.7 cm after discontinuation of therapy ($P < 0.01$). Height SD scores for BA tended to normalize from −1.74 ± 1.15 at start to −1.19 ± 1.2 SD at the end of CPA therapy ($P < 0.05$).

The validity of all these findings concerning better height predictions by CPA treatment are difficult to evaluate since the final heights eventually achieved have not been reported.

Conclusions

Statural growth may be regarded as a combination between how fast the bones are maturing and how fast the body is growing. Statural growth in patients with precocious puberty will not be improved as long as skeletal maturation and growth velocity cannot be kept at a normal rate (i.e. ratio ΔBA/CA about 1 or less, and velocity score for BA ≥ 0) until final height has been achieved.

The patients with the more severe deviation from normal at the beginning of therapy who were treated with 'high' doses of CPA tended to react faster than the 'low' dose treated subjects. This would mean that the speed of reducing accelerated bone maturation and growth velocity might depend on the dosage, i.e. 'high' dose therapy works faster. On the other hand, the therapeutic effect might have been more pronounced the more severely affected the patients were.

The suppression of gonadotropins and sexual steroids is a highly desirable effect of CPA in the treatment of IPP. Moreover, it might be speculated that despite the adrenal hypofunction, the glucocorticoid-like properties (Girard et al. 1978) of CPA cause a condition similar to Cushing's disease which would explain why positive effects on growth are missing.

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